METHODS FOR CONTROLLING FUNGI AND BACTERIA

[0001] CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to United States Provisional Application No. 60/480,995, filed on June 23, 2003, United States Provisional Application No. 60/524,775, filed on November 25, 2003, United States Provisional Application No. 60/525,075, filed on November 25, 2003, United States Provisional Application No. 60/524,784, filed on November 25, 2003, and United States Provisional Application No. 60/450,599, filed on March 3, 2003, the disclosures of which are incorporated herein by reference in their entireties.

[0003] FIELD OF THE INVENTION

[0004] The present invention generally relates to methods of controlling fungi and/or bacteria. More specifically the present invention relates to controlling fungal or bacterial infestations relating to agricultural uses.

[0005] BACKGROUND OF THE INVENTION

[0006] Fungi includes organisms such as slime molds, mushrooms, smuts, rusts, mildews, molds, stinkhorns, puffballs, truffles and yeasts. Fungi are classified in their own kingdom because they absorb food in solution directly through their cell walls and reproduce through spores. Molds are a large group of fungi that are a common trigger for allergies and affect crops, plants and food. Molds can exist as tiny particles called "mold spores" present in indoor and outdoor air. There are more than 100,000 species in the world. Molds may grow anywhere they can find moisture sources. Common molds include Cladosporium, Penicillium, Aspergillus, Alternaria, Fusarium, Neurospora, Stachybotyrs and Mucor.

[0007] Soil-borne and seed-borne fungal pathogens of plants are responsible for severe economic losses in the agricultural and horticultural industries worldwide. These pathogens cause plant diseases such as seed decay, root/foot rot, seedling blight and wilt. Such diseases commonly reduce emergence, plant vigor and yield potential. Severe disease infection can kill emerging seedlings of an entire plant population, and result in a total loss of crop yield.

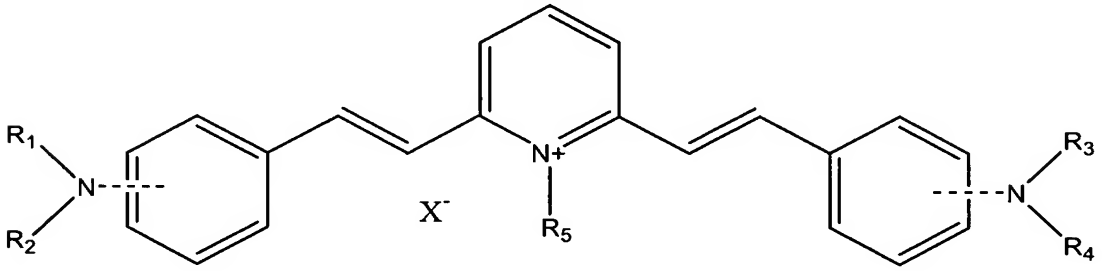
[0008] Solutions to the recurring problem of plant pathogens have been explored for decades. As particular crops become more abundant, and the area of land allocated for agriculture expands, there is an inherent need to employ more efficient and effective farming practices. As a result of increasing demand for crop production, farmers must often

compromise their cultural practices by planting crops on sub-optimal land, or by increasing the frequency at which crops are planted in a specific location. In doing so, crop nutrients are depleted and specific crop pathogens, especially soil-borne or seed-borne pathogens, become more prevalent. Accordingly, it is increasingly difficult to sustain the health and productivity of a respective crop.

[0009] Stilbazium iodide is a known anthelmintic which is reported to be effective against roundworms, threadworms, and whipworms. US Patent No. 3,075,975 and U.S. Patent No. 3,085,935 recite methods of eradicating infestations of parasitic nematodes inhabiting the intestinal tract.

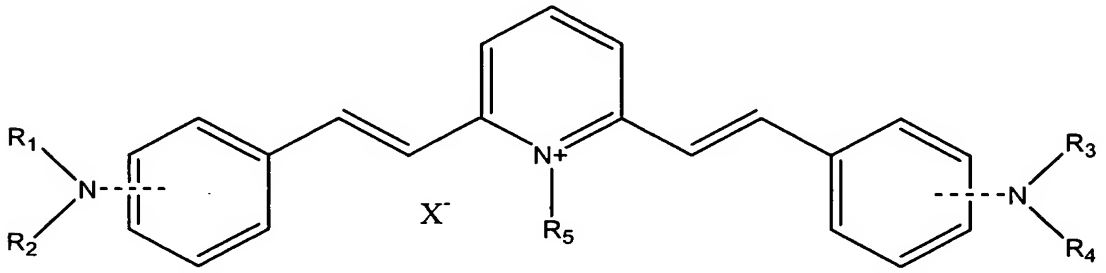
[00010] SUMMARY OF THE PRESENT INVENTION

[00011] The present invention relates to methods and compositions comprising stilbazium. One aspect of the present invention is a composition comprising formula (I)



or a solvate thereof wherein said compound is substantially in the E, E configuration. The amino moieties may be in either the ortho, meta or para postions. X^- may be an anionic salt, R_1, R_2, R_3, or R_4 are independently selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), or wherein R_1 and R_2 or R_3 and R_4 taken together with the nitrogen atom to which they are attached form pyrrolidino or piperidino rings; and R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. The substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties may include, but are not limited to lower alkyl, aryl, benzyl, acyl, amido, amino, alkoxy, carboxy, carboxy ester, alcohol, nitro, trifluoroalkoxy, trifluoroalkyl and halo. R_5 may also be an organometallic compound such as organotin, organosilicon, or organogermanium. Additionally, R_5 may be $(CH_2)_n$-MR_6, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R_6 is a selected from the group consisting of propyl, butyl, or any alkyl compound.

[00012] The present invention also relates to methods of controlling fungi and/or bacteria comprising administering a composition comprising any of the below formulas or a solvate thereof.



or a solvate thereof, wherein X^- is an anionic salt, wherein R_1, R_2, R_3, or R_4 are independently selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), or wherein when R_1 and R_2 or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form pyrrolidino or piperidino rings. R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. R_5 may also be an organometallic compound such as organotin, organosilicon, or organogermanium. Additionally, R_5 may be $(CH_2)_n$-MR_6, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R_6 is a selected from the group consisting of propyl, butyl, or any alkyl compound. The present compound is more commonly known as stibazium.

[00013] BRIEF DESCRIPTION OF THE DRAWINGS

[00014] FIGs. 1A-1G show various compounds including a methyl on a pyridine ring at the nitrogen position.

[00015] FIGs. 2A-2G depict various compounds including a trifluoroethyl attached to the pyridine ring at the nitrogen position.

[00016] FIGs. 3A-3F illustrate compounds including an isobutyl on the pyridine ring at the nitrogen position.

[00017] FIGs. 4A-4G depict various compounds with an ethyl attached to the pyridine ring at the nitrogen position.

[00018] DETAILED DESCRIPTION OF THE EMBODIMENTS OF THE INVENTION

[00019] The foregoing and other aspects of the present invention will now be described in more detail with respect to other embodiments described herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

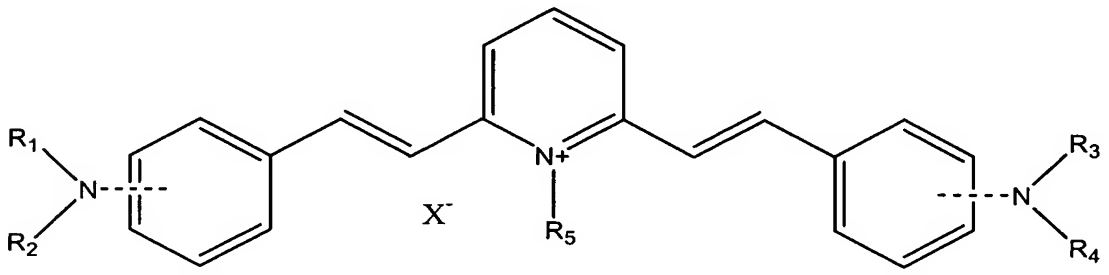
[00020] The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

[00021] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[00022] All publications, patent applications, patents and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

[00023] The present invention relates to pyridinium derivatives, processes for their preparation, methods of their use and compositions comprising such derivatives. Stilbazium iodide is a known anthelmintic which is reported to be effective against roundworms, threadworms, and whipworms. U.S. Patent Nos. 3,075,975 and 3,085,935 recite methods of eradicating infestations of parasitic nematodes inhabiting the intestinal tract. This compound can be used to control fungi and/or bacteria in both industrial and agricultural uses.

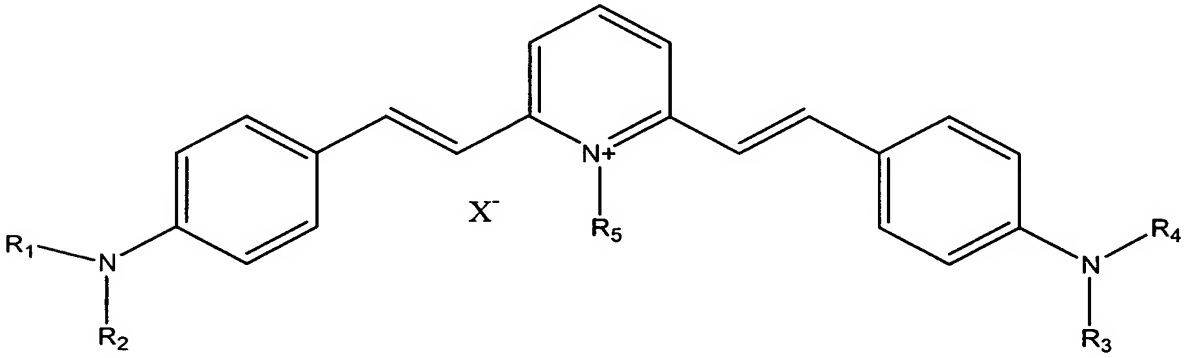
[00024] One of the embodiments of the present invention includes a compound comprising:



or a solvate thereof, wherein X^- is an anionic salt, wherein R_1, R_2, R_3, or R_4 are independently selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes

(linear or branched), alkenes, or wherein when R_1 and R_2 or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form pyrrolidino or piperidino rings. X^- can be selected from the group including fluoride, chloride, bromide, iodide halide, mesylate, tosylate, napthylate, nosylate, para-aminobenzoate, lauryl sulfate, 2,4-dihydroxy benzophenone, 2-(2-hydroxy-5'-methylphenyl) benzotriazole, benzenesulfonate, besylate, ethyl 2-cyano-3,3-diphenyl acrylate and 5-butyl phenyl salicylate. R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. R_5 may also be an organometallic compound such as organotin, organosilicon, or organogermanium. Additionally, R_5 may be $(CH_2)_n$-MR_6, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R_6 is a selected from the group consisting of propyl, butyl, or any alkyl compound.

[00025] Another embodiment of the present invention includes a compound comprising formula (II)

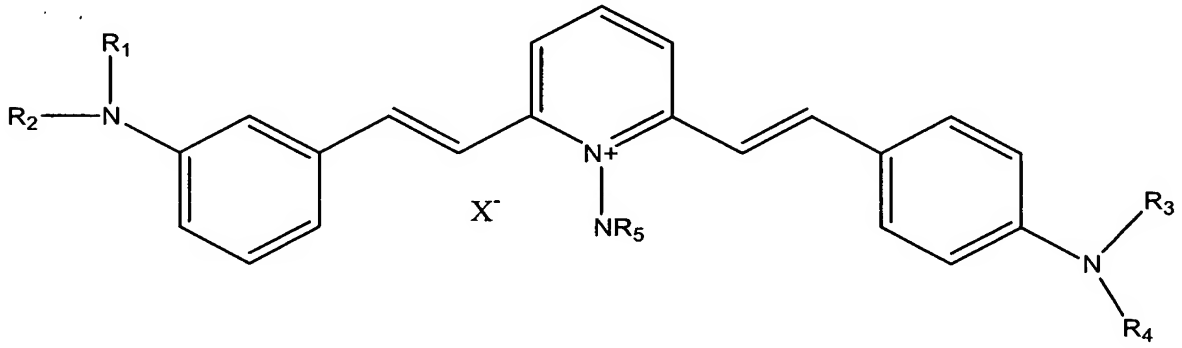


or a solvate thereof, wherein X^- is an anionic salt, wherein R_1, R_2, R_3, or R_4 are independently selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), or wherein when R_1 and R_2 or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form pyrrolidino or piperidino rings. X^- can be selected from the group including fluoride, chloride, bromide, iodide halide, mesylate, tosylate, napthylate, nosylate, para-aminobenzoate, lauryl sulfate, 2,4-dihydroxy benzophenone, 2-(2-hydroxy-5'-methylphenyl) benzotriazole, benzenesulfonate, besylate, ethyl 2-cyano-3,3-diphenyl acrylate and 5-butyl phenyl salicylate. R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. R_5 may also be an organometallic compound such as organotin, organosilicon, or organogermanium.

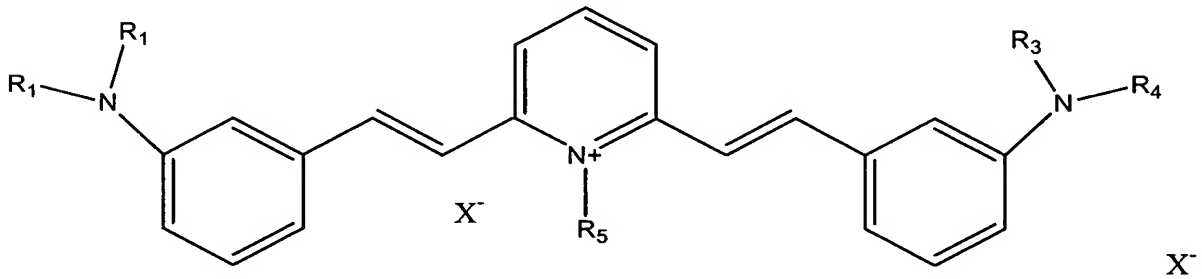
Additionally, R_5 may be $(CH_2)_n$-MR_6, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R_6 is a selected from the group consisting of propyl, butyl, or any alkyl compound. The present compound is more commonly known as stibazium. One of the embodiments of formula I is 2,6,-bis (p-pyrrolidinostyryl) pyridine methiodide.

[00026] Alternatively, the NR_1 moiety may be in various positions as evidenced in the compounds below.

[00027] Another embodiment includes Formula III illustrates the NR_1 moiety in one meta position.

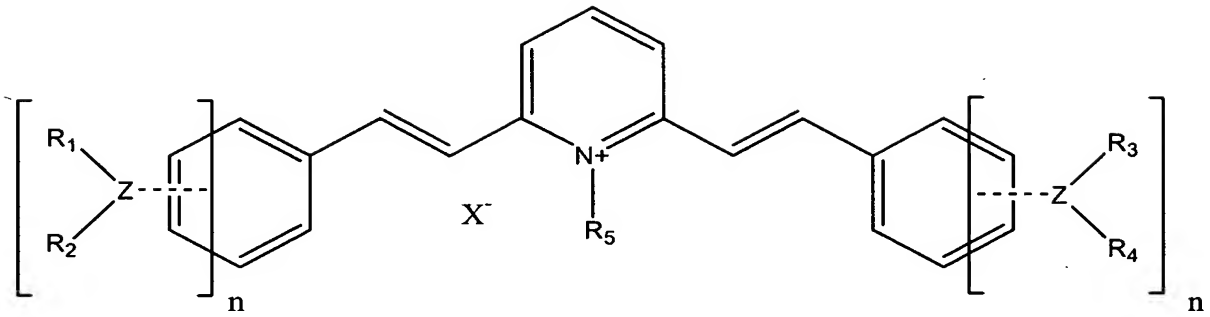


[00028] Formula IV illustrates the NR_1 moiety in both meta positions.



may be an anionic salt, R_1, R_2, R_3, or R_4 are independently selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), or wherein when R_1 and R_2 or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form pyrrolidino or piperidino rings. R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties.

[00029] Additionally, the present invention may include compounds of the following general formula V:



or a solvate thereof, wherein n is a number from 1 to 5, wherein Z can be present at multiple positions on the phenyl ring and is selected from the group consisting of C, N, O, S and halogen, wherein X^- is an anionic salt, wherein R_1, R_2, R_3, or R_4 are independently selected from the group consisting of nothing, hydrogen, methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), nitriles, benzenes, pyridines, benzothiophenes, trifluoroalkyls, difluoroalkyls, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties, or wherein when R_1 and R_2 or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form pyrrolidino or piperidino rings. X^- can be selected from the group including fluoride, chloride, bromide, iodide halide, mesylate, tosylate, napthylate, nosylate, para-aminobenzoate, benzenesulfonate, besylate, lauryl sulfate, 2,4-dihydroxy benzophenone, 2-(2-hydroxy-5'-methylphenyl) benzotriazole, ethyl 2-cyano-3,3-diphenyl acrylate and 5-butyl phenyl salicylate. R_5 is selected from the group consisting of methyl, ethyl, C_{1-10} alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. R_5 may also be an organometallic compound such as organotin, organosilicon, or organogermanium. Additionally, R_5 may be $(CH_2)_n$-MR_6, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R_6 is a selected from the group consisting of propyl, butyl, or any alkyl compound. FIGs. 1-4 illustrate various combinations of the compounds that may be formed according to the present invention. These compounds can be in the E, E configuration and can be used for any of the methods and uses disclosed in the present application.

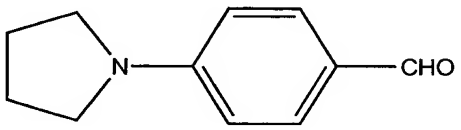
[00030] The compounds of the present invention are capable of existing as geometric isomers. All such isomers, individually and as mixtures, are included within the scope of the present invention for their agricultural uses. The *E,E* isomer is one configuration of the invention, and both the *cisoid* and *transoid* 2,6-conformations of the E,E-configuration are possible. Additionally, the otho, ortho conformation of the structure can be formed in

addition to the para and meta structures illustrated above. The ortho conformation structure can include the same salts and moieties as disclosed above and throughout the application.

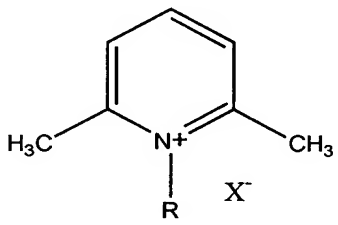
[00031] Some of the embodiments of the present invention include 1-ethyl-(*E-E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride, 1-ethyl-(*E-E*)-2,6-bis[p-(1-pyrrolidinostyryl]pyridinium chloride, 1-methyl-(*E-E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride and 1-methyl-(*E-E*)-2,6-bis[p-(1-pyrrolidinostyryl]pyridinium chloride.

[00032] Compounds according to the invention can be made according to any suitable method of organic chemistry. More specifically, compounds of formula I can be prepared as outlined in U.S. Patent No. 3,085,935, the disclosure of which is incorporated in its entirety.

[00033] Additionally, embodiments of the present invention may include the compounds produced by a synthesis that includes preparing the compounds by condensation of two equivalents of an aldehyde of formula VI.



with a quatenary ammonium salt of 2,6-lutidine



[00034] The condensation may be performed in a lower alcohol with a catalyst such as a secondary amine (e.g. piperidine). When X^- in the above formula is an iodide ion (corresponding to an alkiodide salt of lutidine), the condensation product (formula I) is relatively insoluble and precipitates in the course of the reaction. The reaction yield of formula I can be nearly quantitative. Three times the amount of catalyst as stated in U.S. Patent 3,085,935 can be used. Other methods may be used to produce the compound and both more or less catalyst may be employed to produce formula I.

[00035] For the above reactions, R can be selected from the group consisting of methyl, ethyl, $C_{1\text{-}10}$ alkyl (linear or branched), alkenes (linear or branched), alkynes, n-propyl, i-

propyl, n-butyl, i-butyl, substituted and unsubstituted aryl moieties and substituted and unsubstituted benzyl moieties. Additionally, R can be $(CH_2)_n$-MR_2, wherein n is a number from 1 to 6, M is an organometallic compound such as tin, silicon, or germanium, and wherein R2 is a selected from the group consisting of propyl, butyl, or any alkyl compound.

[00036] Alternatively, the compound can be prepared by dissolving 2,6-lutidine ethiodide in methanol, followed by bubbling anhydrous HCl (220grams) slowly into the solution. An ice/H2O bath can be used to keep the reaction below 30°C. After all the HCl has been added, the reaction is stirred overnight at room temperature. After stirring, the reaction should be concentrated to near dry and re-diluted with 1000mL of fresh methanol. The ethiodide can be converted to the desired ethochloride by bubbling anhydrous HCl into the mixture. After stirring 10 minutes, the reaction is concentrated to dry on a rotovap, and placed on hi-vacuum manifold for final drying overnight.

[00037] Another embodiment of the present invention can include the stibazium compounds being encapsulated. As used herein the term "microcapsules" is intended to contemplate single molecules, encapsulated discrete particulate, multiparticulate, liquid multicore and homogeneously dissolved active components. The encapsulation method may provide either a water soluble or oil soluble active component encapsulated in a shell matrix of either a water or oil soluble material. The microencapsulated active component may be protected from oxidation and hydration, and may be released by melting, rupturing, biodegrading, or dissolving the surrounded shell matrix or by slow diffusion of the active component through the matrix. Microcapsules usually fall in the size range of between 1 and 2000 microns, although smaller and larger sizes are known in the art.

[00038] The compound of the present invention may be placed in a microcapsule or hollow fiber type used for distribution. They may also be dispersed in a polymeric material or held as a liquid.

[00039] An active ingredient may be placed with the compound of the present invention in a microcapsule. Examples of the active ingredient having repellent activity may include triethylene glycol monohexyl ether and N,N-diethyl-m-triamide. Examples of the active ingredient having aromatic activity include geraniol, limonene, benzyl alcohol, esters of a C_{6-20} hydrocarbon, ethers, aldehydes and alcoholic compounds. Examples of the active ingredient having pesticidal activity include insecticides such as salithion, diazinon and chlorpyrifos and bactericides such as thiophanate-methyl and captan.

[00040] Such constituents can be encapsulated, as is desired in the case of phase change materials. Such encapsulated constituents can further be encapsulated in microcapsules. The microcapsules can be made from a wide variety of materials, including polyethylene,

polypropylenes, polyesters, polyvinyl chloride, tristarch acetates, polyethylene oxides, polypropylene oxides, polyvinylidene chloride or fluoride, polyvinyl alcohols, polyvinyl acetates, urethanes, polycarbonates, and polylactones. Further details on microencapusulation are to be found in U.S. Pat. Nos. 5,589,194 and 5,433,953, the contents of which are incorporated herein in their entirety. Microcapsules suitable for use in the base materials of the present invention have diameters from about 1.0 to 2,000 microns.

[00041] No particular limitation is imposed on the shape for holding the active ingredient. In other words, there are various forms for holding the active ingredient by a holding mixture. Specific examples include microcapsules in which the surface of the active ingredient has been covered with the holding mixture; and products processed into a desired shape, each being obtained by kneading the active ingredient in the holding mixture or forming a uniform solution of the holding mixture and the active ingredient, dispersing the active ingredient in the holding mixture by the removal of the solvent or the like and then processing the dispersion into a desired shape such as single molecule, liquid, sphere, sheet, film, rod, pipe, thread, tape or chip. In addition, these processed products having a surface covered with a barrier layer for controlling the release of the active ingredient and those coated with an adhesive for improving applicability can be given as examples. As further examples, those obtained by filling the active ingredient in the holding mixture processed into a form of a capillary tube, heat sealing both ends of the capillary tube and then encapsulating the active ingredient therein; and those obtained by centrally cutting the above-mentioned capillary tube into two pieces, thereby having each one end as an opening.

[00042] The container formed of a holding mixture which container has an active ingredient enclosed therein as a liquid phase to secure uniform release ability over a long period of time. As such shape, tube-, bottle- or bag-shaped container is used generally.

[00043] When the mixture is formed into a container, the sustained release layer desirably has a thickness of at least 0.002 mm for effecting stable sustained release. There occurs no particular problem when the sustained release layer has a thickness not smaller than 0.002 mm, but that ranging from 0.005 mm to 5 mm can be used. When it exceeds 5 mm, the release amount of the compound tends to become too small.

[00044] For solids, the release surface area of the sustained release preparation formed of such a container is desirably .001 cm^2 or larger. A range of from .01 cm^2 to 1 cm^2 may be used.

[00045] When the active ingredient is enclosed and held in a container of the sustained release preparation, said container having been formed of a holding mixture, it may be

enclosed in portions. The enclosed amount can be 0.5mg to 5 mg, and may be 1mg, 2mg, 3mg, or 4mg.

[00046] As the shape of the container formed of a holding mixture, a tube, bottle and bag can be used. In the case of the tube-shaped preparation, that having an internal diameter of 0.4 mm to 10 mm can be used. Internal diameters smaller than 0.4 mm make it difficult to fill the active ingredient in the container, while those larger than 10 mm make it difficult to conduct encapsulation. The bottle-shaped preparation is formed by blow molding or injection molding and generally has an internal volume of 0.1 to 200 ml. The bottle having an internal volume less than 0.1 ml cannot be formed easily, while that having an internal volume greater than 200 ml is not economical because there is a large difference between the amount of the active ingredient filled therein and the internal volume. In the case of a bag-shaped preparation, the amount of the active ingredient filled in the bag is desirably 1 mg to 100 g.

[00047] The biodegradable sustained-release preparation according to the first group of the present invention should retain its essential performance during application so that a pigment or dye, or various stabilizers such as ultraviolet absorber/blocker or antioxidant may be added to the holding mixture in order to improve the weather resistance. Alternatively, it is possible to add such an additive to the active ingredient enclosed in the container formed of a holding mixture.

[00048] As used herein, the term "controlled release" is intended to mean the release of a bio-active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release profiles. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of the bio-active are also contemplated by the present invention.

[00049] As used herein, the term "bio-active" includes therapeutic agents such as pharmaceutical or pharmacological active agents, e.g., drugs and medicaments, as well as prophylactic agents, diagnostic agents and other chemicals or materials useful in treating or preventing conditions, infections and/or diseases. The compositions of the present invention are particularly effective in plants and other organisms.

[00050] In accordance with the present invention there is provided a microcapsule bacteriocide and/or fungicide composition comprising microcapsules each having a polyurea shell including as an integral part of said shell a photostable ultraviolet light absorbent compound or blocker compound having a log molar extinction coefficient of from about 2 to 5 with respect to radiation having wave lengths in the range of from about 270 to 350

nanometers and a liquid fill capable of slowly permeating the shell and comprising a pyridinium salt and a biological synergist therefor.

[00051] As used herein "photosensitive material" refers to all compositions and materials designed to block and/or absorb ultraviolet light. This term also refers to all photoprotective and photoresistant agents.

[00052] As herein used "surfactant" refers to all compositions including surfactant salt compositions that are capable of forming emulsions, micro-emulsions, suspensions, etc.

[00053] The entire microcapsule composition can include of 60-90 percent of liquid fill and 40-10 percent of shell wall, the liquid fill comprising 5-40 percent of pyridinium salt, 25-50 percent of biological synergist and 20-40 percent of a water-immiscible organic solvent and the shell including as an integral part thereof 0.5-20 percent of photostable ultraviolet light absorbent compound (all percentages being based on the weight of the entire microcapsule composition).

[00054] The pyridinium salt remains inside the microcapsules while the composition is packaged and in storage, *i.e.*, in a closed container due to the partial pressure of the pyridinium salt surrounding the microcapsules. When the product is applied as a bacteriocide and/or fungicide, the pyridinium salt, releases slowly (the actual speed of release depending upon the thickness and porosity of the capsule walls). The pyridinium salt is chemically stable during storage and after application until it permeates the capsule walls. At that time it becomes available as a bacteriocide and/or fungicide until degraded. Since the fill permeates the shell wall slowly, the microcapsule product has a long effective bacteriocide and/or fungicide life and may be stored for extended periods (e.g. for 6 months and more).

[00055] Suitable fill stabilizers absorb ultraviolet radiation in the range of about 270-350 nanometers and convert it to a harmless form. They have a high absorption coefficient in the near ultraviolet portion of the spectrum (e.g. a log molar extinction coefficient of from about 2 to 5) but only minimal absorption in the visible portion of the spectrum. They do not exhibit any substantial chemical reaction with the isocyanate groups and primary amine groups of the shell forming compounds during the microencapsulation process. Among the compounds which can be used as fill stabilizers are substituted benzophenones such as 2,4-dihydroxy benzophenone, 2-hydroxy-4-methoxy benzophenone, 2-hydroxy-4-octyloxy benzophenone, etc.; the benzotriazoles such as 2-(2-hydroxy-5'-methylphenyl) benzotriazole, 2-(3',5'-diallyl-2'-hydroxylphenyl)benzotriazole, etc.; substituted acrylates such as ethyl 2-cyano-3,3-diphenyl acrylate, 2-ethylhexyl-2-cyano-3,3-diphenyl acetate, etc.; salicylates such as phenyl salicylates, 5-butyl phenyl salicylate, etc.; and nickel organic compounds such as nickel bis (octylphenol) sulfide, etc. Additional examples of each of these classes of fill

stabilizers may be found in Kirk-Othmer, Encyclopedia of Chemical Technology. The fill stabilizers may comprise up to 5 percent, and are generally from about 0.01 to 2 percent, by weight of the microcapsule composition.

[00056] The embodiments of the invention also provide a process for controlling fungal and bacterial activity by contacting the fungi and bacteria with an effective level of the compositions comprising stilbazium compound as recited throughout. Contact may be accomplished directly, for example, by atomization of the composition into the air in the form of a spray. Alternatively, compositions of the present invention may be provided in various other forms, for example in sheet materials carrying the microcapsules, (e.g. tapes coated or impregnated with the microcapsules) that may be placed in areas where the fungi and bacteria may grow.

[00057] Another embodiment of the present invention may include heat sensitive materials which are excellent in preservation stability especially in resistance to light, and microcapsules having an ultraviolet absorber enclosed therein, which are applicable to various fields. Desirable constituents which may be present in a base material include materials which can absorb heat and protect an underlying material from overheating. Thermal energy is absorbed by the phase change of such materials without causing an increase in the temperature of these materials. Suitable phase change materials include paraffinic hydrocarbons, that is, straight chain hydrocarbons represented by the formula C_nH_{n+2}, where n can range from 13 to 28. Other compounds which are suitable for phase change materials are 2,2-dimethyl-1,3-propane diol (DMP), 2-hydroxymethyl-2-methyl-1,3-propane diol (HMP) and similar compounds. Also useful are the fatty esters such as methyl palmitate. Phase change materials that can be used include paraffinic hydrocarbons.

[00058] Heat sensitive recording materials are well known which utilize a color forming reaction between a colorless or light-colored basic dye and an organic or inorganic color acceptor to obtain record images by thermally bringing the two chromogenic substances into contact with each other. Such heat sensitive recording materials are relatively inexpensive, are adapted for use with recording devices which are compact and easy to maintain, and have therefore found wide applications as recording media for facsimile systems, various computers, etc. In order to improve light resistance of heat sensitive recording materials a finely divided ultraviolet absorber or blocker can be added to the heat sensitive recording layer or protective layer.

[00059] Another embodiment of the present invention is to provide microcapsules which have excellent retainability of ultraviolet absorber, difficult to be ruptured at a usual pressure and are excellent in ultraviolet ray absorbing efficiency.

[00060] Embodiments of the present invention can include a heat sensitive recording material comprising a substrate, a recording layer formed over the substrate and containing a colorless or light-colored basic dye and a color acceptor, and a protective layer formed over the recording layer, the recording material being characterized in that microcapsules having an ultraviolet absorber enclosed therein and having substantially no color forming ability are incorporated in the protective layer.

[00061] Further, the present invention provides microcapsules having an ultraviolet absorber and as required an organic solvent enclosed therein, which have capsule wall film of synthetic resin and mean particle size of 0.1 to 3μm.

[00062] The following are examples of ultraviolet absorbers that may be used in the present invention.

[00063] Phenyl salicylate, p-tert-butylphenyl salicylate, p-octylphenyl salicylate and like salicylic acid type ultraviolet absorbers; 2,4-dihydroxybenzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-octyloxybenzophenone, 2-hydroxy-4-dodecyloxybenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone, 2,2,'-dihydroxy-4,4'-dimethoxybenzophenone, 2-hydroxy-4-methoxy-5-sulfobenzophenone and like benzophenone type ultraviolet absorbers; 2-ethylhexyl 2-cyano-3,3-diphenyt-acrylate, ethyl 2-cyano-3,3-diphenylacrylate and like cyanoacrylate type ultraviolet absorbers; bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate, bis(2,2,6,6-tetramethyl-4-piperidyl) succinate, bis(1,2,2,6,6-pentamethyl-4-piperidyl) 2-(3,5-di-tert-butyl-4-hydroxybenzyl)-2-n-butyl malonate and like hindered amine type ultraviolet absorbers; 2-(2'-hydroxyphenyl)benzotriazole, 2-(2'-hydroxy-5'-methylphenyl)benzotriazole, 2- (2'-hydroxy-5 -tert-butylphenyl)benzotriazole, 2- (2'-hydroxy-3',5'-di-tert-butylphenyl)benzotriazole, 2- (2'-hydroxy-3'-tert-butyl-5'-methylphenyl)-5-chlorobenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)-5-chlorobenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)-5-tert-butylbenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-amylphenyl)benzotriazole, 2-(2'-hydroxy-3',5'-di-tert-amylphenyl)-5-tert-amylbenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-amylphenyl)-5-methoxybenzotriazole, 2-[2'-hydroxy-3'-(3",4",5",6"-tetrahydrophthalimido-methyl)-5'-methylpheny l]benzotriazole, 2-(2'-hydroxy-5'-tert-octylphenyl)benzotriazole, 2-(2'-hydroxy-3'-sec-butyl-5'-tert-butylphenyl)benzotriazole, 2-(2'-hydroxy-3'-tert-amyl-5'-phenoxyphenyl)-5-methylbenzotriazole, 2-(2'-hydroxy-5'-n-dodecylphenyl)benzotriazole, 2-(2'-hydroxy-5'-sec-octyloxyphenyl)-5-phenylbenzotriazole, 2-(2'-hydroxy-3'-tert-amyl-5'-phenylphenyl)-5-methoxybenzotriazole, 2-[2'-hydroxy-3',5'-bis(α,α-dimethylbenzyl)phenyl]benzotriazole and like benzotriazole type ultraviolet absorbers which are solid at ordinary temperature; 2-(2'-Hydroxy-3'-dodecyl-5'-methylphenyl)-benzotriazole, 2-(2'-hydroxy-3'-undecyl-5'-

methylphenyl)-benzotriazole, 2-(2'-hydroxy-3'-tridecyl-5'-methylphenyl)-benzotriazole, 2-(2'-hydroxy-3'-tetradecyl-5'-methylphenyl)-benzotriazole, 2-(2'-hydroxy-3'-pentadecyl-5'-methylphenyl)-benzotriazole, 2-(2'-hydroxy-3'-hexadecyl-5'-methylphenyl)-benzotriazole, 2-[2'-hydroxy-4'-(2"-ethylhexyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(2"-ethylheptyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(2"-ethyloctyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(2"-propyloctyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(2"-propylheptyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(2"-propylhexyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(1"-ethylhexyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(1"-ethylheptyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(1"-ethyloctyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy-4'-(1"-propyloctyl)oxyphenyl] -benzotriazole, 2-[2'-hydroxy-4'-(1"-propylheptyl)oxyphenyl]-benzotriazole, 2-[2'-hydroxy4'-(1"-propylhexyl)oxyphenyl]-benzotriazole, 2-(2'-hydroxy-3'-sec-butyl-5'-tert-butylphenyl-5-n-butylbenzotriazole, 2-(2'-hydroxy-3'-sec-butyl-5'-tert-butylphenyl) -5-tert-pentyl-benzotriazole, 2-(2'-hydroxy-3'-sec-butyl-5'-tert-butylphenyl)-5-n-pentyl-benzotriazole, 2-(2'-hydroxy-3'-sec-butyl-5'-tert-pentylphenyl)-5-tert-butylbenzotriazole , 2-(2'-hydroxy-3'-sec-butyl-5'-tert-pentylphenyl)-5-n-butylbenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-butylphenyl)-5-sec-butylbenzotriazole, 2-(2'-hydroxy-3',5'-di-tert-pentylphenyl)-5-sec-butylbenzotriazole, 2-(2'-hydroxy-3'-tert-butyl-5'-tert-pentylphenyl)-5-sec-butylbenzotriazole , 2-(2'-hydroxy-3',5'-di-sec-butylphenyl)-5-chlorobenzotriazole, 2-(2'-hydroxy-3',5'-di-sec-butylphenyl)-5-methoxybenzotriazole, 2-(2'-hydroxy-3',5'-di-sec-butylphenyl)-5-tert-butylbenzotriazole, 2-(2'-hydroxy-3',5'-di-sec-butylphenyl)-5-n-butylbenzotriazole, octyl 5-tert-butyl-3-(5-chloro-2H-benzotriazole-2-yl)-4-hydroxybenzene-propionate, condensate of methyl 3-[3-tert-butyl-5-(2H-benzotriazole-2-yl)-4-hydroxyphenyl]propionate and polyethylene glycol (molecular weight: about 300) and like benzotriazole type ultraviolet absorbers which are liquid at ordinary temperature. Of course, the ultraviolet absorber is not limited to thereabove and can be used as required in a mixture of at least two of them.

[00064] Although the amount of ultraviolet absorber to be used is not limited specifically, the amount can be adjusted to 10 to 500 parts by weight, and generally from to 20 to 250 parts by weight.

[00065] The microcapsules for use in the present invention can be prepared by various known methods. They are prepared generally by emulsifying and dispersing the core material (oily liquid) comprising an ultraviolet absorber and, if necessary, an organic solvent in an aqueous medium, and forming a wall film of high-molecular-weight substance around the resulting oily droplets.

[00066] Examples of useful high-molecular-weight substances for forming the wall film of microcapsules are polyurethane resin, polyurea resin, polyamide resin, polyester resin, polycarbonate resin, aminoaldehyde resin, melamine resin, polystyrene resin, styrene-acrylate copolymer resin, styrene-methacrylate copolymer resin, gelatin, polyvinyl alcohol, etc. Especially, microcapsules having a wall film of a synthetic resin, particularly polyurea resin, polyurethane resin and aminoaldehyde resin among other resins have excellent retainability of an ultraviolet absorber and high heat resistance and accordingly exhibit the outstanding additional effect to serve the function of a pigment which is to be incorporated in the protective layer for preventing sticking to the thermal head. Moreover, microcapsules having a wall film of polyurea resin or polyurethane resin are lower in refractive index than microcapsules with wall films of other materials and usual pigments, are spherical in shape and are therefore usable favorably because even if present in a large quantity in the protective layer, they are unlikely to reduce the density of record images (so-called whitening) owing to irregular reflection of light. Further, polyurea resin and polyurethane resin are more elastic than aminoaldehyde resin and therefore polyurea resin and polyurethane resin are generally used as a wall film for microcapsules which are used under a condition of high pressure. On the other hand, microcapsules having a wall film made from aminoaldehyde resin have a merit that the wall film can be controlled in thickness without depending on particle size of emulsion because the microcapsules can be prepared by adding a wall-forming material after emulsification of a core material.

[00067] The present invention may also include organic solvent together with an ultraviolet absorber. The organic solvent is not particularly limited and various hydrophobic solvents can be used which are used in a field of pressure sensitive manifold papers. Examples of organic solvents are tricresyl phosphate, octyldiphenyl phosphate and like phosphates, dibutyl phthalate, dioctyl phthalate and like phthalates, butyl oleate and like carboxylates, various fatty acid amides, diethylene glycol dibenzoate, monoisopropylnaphthalene, diisopropylnaphthalene and like alkylated naphthalenes, 1-methyl-1-phenyl-1-tolylmethane, 1-methyl-1-phenyl-1-xylylmethane, 1-phenyl-1-tolylmethane and like alkylated benzenes, isopropylbiphenyl and like alkylated biphenyls, trimethylolpropane triacrylate and like acrylates, ester of polyols and unsaturated carboxylic acids, chlorinated paraffin and kerosene. These solvents can be used individually or in a mixture of at least two of them. Among these hydrophobic media having a high boiling point, tricresyl phosphate and 1-phenyl-1-tolylmethane are desirable since they exhibit high solubility in connection with the ultraviolet absorber to be used in the present invention. Generally, the lower the viscosity of the core material, the smaller is the particle size

resulting from emulsification and the narrower is the particle size distribution, so that a solvent having a low boiling point is conjointly usable to lower the viscosity of the core material. Examples of such solvents having a low boiling point are ethyl acetate, butyl acetate, methylene chloride, etc.

[00068] The amount of organic solvent to be used should be suitably adjusted according to the kind and amount of ultraviolet absorber to be used and the kind of organic solvent and is not limited specifically. For example in case of using an ultraviolet absorber which is liquid at ordinary temperature, an organic solvent is not necessarily used. However, in case of using an ultraviolet absorber which is solid at ordinary temperature, since it is desired that the ultraviolet absorber be in a fully dissolved state in the microcapsules, the amount of organic solvent, for example in case of microcapsules of polyurea resin or polyurethane resin, is adjusted generally from to usually 10 to 60 wt. %, or from to 20 to 60 wt. %, based on the combined amount of organic solvent, ultraviolet absorber and wall-forming material. Further, in case of microcapsules of aminoaldehyde resin, the amount of organic solvent is adjusted to usually 50 to 2000% by weight, generally from 100 to 1000% by weight of ultraviolet absorber.

[00069] Additionally, an absorber may be utilized. An absorber should be selected which reduces the sensitivity of the microcapsule in those portions of its spectral sensitivity range which interfere with the exposure of microcapsules at other wavelengths (its inactive range) without overly reducing the sensitivity of the microcapsule in those portions of the spectral sensitivity range in which the microcapsule is intended to be exposed (its active range). In some cases it may be necessary to balance the absorption characteristics of the absorber in the active range and the inactive range to achieve optimum exposure characteristics. Generally absorbers having an extinction coefficient greater than about 100/M cm in the inactive range and less than about 100,000/M cm in the active range of the microcapsule are used. When the absorber is directly incorporated into the photosensitive composition, ideally, it should not inhibit free radical polymerization, and it should not generate free radicals upon exposure.

[00070] The absorbers used in the present invention can be selected from among those absorbers which are known in the photographic art. Examples of such compounds include dyes conventionally used as silver halide sensitizing dyes in color photography (e.g., cyanine, merocyanine, hemicyanine and styryl dyes) and ultraviolet absorbers. A number of colored dyes which absorb outside the desired sensitivity range of the microcapsules and do not absorb heavily within the range could also be used as absorbers in the present invention.

Among these, Sudan I, Sudan II, Sudan III, Sudan Orange G, Oil Red O, Oil Blue N, and Fast Garnet GBC are examples of potentially useful compounds.

[00071] Additionally ultraviolet absorbers that may be desirable include those selected from hydroxybenzophenones, hydroxyphenylbenzo-triazoles and formamidines. The absorbers may be used alone or in combination to achieve the spectral sensitivity characteristics that are desired.

[00072] Representative examples of useful hydroxybenzophenones are 2-hydroxy-4-n-octoxybenzophenone (UV-CHEK AM-300 from Ferro Chemical Division, Mark 1413 from Argus Chemical Division, Witco Chem. Corp., and Cyasorb UV-531 Light Absorber from American Cyanamid), 4-dodecyl-2-hydroxybenzophenone (Eastman Inhibitor DOBP from Eastman Kodak), 2-hydroxy-4-methoxybenzophenone (Cyasorb UV-9 Light Absorber from American Cyanamid), and 2,2'-dihydroxy-4-methoxybenzophenone (Cyasorb UV-24 Light Absorber from American Cyanamid). Representative examples of useful hydroxybenzophenyl benzotriazoles are 2-(2'-hydroxy-5'-methylphenyl)benzotriazole (Tinuvin P from Ciba-Geigy Additives Dept.), 2-(3',5'-ditert-butyl-2'hydroxyphenyl)-5-chlorobenzotriazole (Tinuvin 327 from Ciba-Geigy), and 2-(2-hydroxy-5-t-octylphenyl)benzotriazole (Cyasorb UV-5411 Light Absorber from American Cyanamid). Representative examples of useful formamidines are described in U.S. Pat. No. 4,021,471 and include N-(p-ethoxy-carbonylphenyl)-N'-ethyl-N'-phenylformamidine (Givsorb UV-2 from Givaudan Corp.). The optimum absorber and concentration of absorber for a particular application depends on both the absorption maximum and extinction coefficient of the absorber candidates and the spectral sensitivity characteristics of the associated photoinitiators.

[00073] Additionally, the microcapsules, photosensitive compositions, image-forming agents, developers, and development techniques described in U.S. Pat. Nos. 4,399,209 and 4,440,846, the contents of which are incorporated and may be used in the present invention.

[00074] The compounds according to the present invention are also particularly effective against powdery mildews and rusts, pyrenophora, rhynchosporium, tapesia, fusarium and leptosphaeria fungi, in particular against pathogens of monocotyledonous plants such as cereals, including wheat and barley. They are furthermore particularly effective against downy mildew species, powdery mildews, leaf spot diseases and rusts in dicotyledonous plants.

[00075] The amount of the compounds of the invention to be applied, will depend on various factors such as the compound employed, the subject of the treatment (substrate, plant, soil, seed), the type of treatment (e.g. spraying, dusting, seed dressing), the purpose of the

treatment (prophylactic or therapeutic), the type of fungi and/or bacteria to be treated and the application time.

[00076] The fungicidal and/or bactericidal combinations are of particular interest for controlling a large number of fungi and/or bacteria in various crops or their seeds, especially wheat, rye, barley, oats, rice, maize, lawns, cotton, soybeans, coffee, sugarcane, fruit and ornamentals in horticulture and viticulture, in vegetables such as cucumbers, beans and cucurbits, and in field crops such as potatoes, peanuts, tobacco and sugarbeets.

[00077] The combinations are applied by treating the fungi and/or bacteria or the seeds, plants or materials threatened by fungus attack, or the soil with a fungicidally and/or bacterially effective amount of the active ingredients.

[00078] The agents may be applied before or after infection of the materials, plants or seeds by the fungi and/or bacteria.

[00079] When applied to the plants the compound of formula I is applied at a rate of 25 to 250 g/ha, generally from 50 to 150 g/ha, e.g. 75, 100, 125 or 150g/ha, in association with 20 to 2000 g/ha, generally from 20 to 1000 g/ha.

[00080] In agricultural practice the application rates of the combination depend on the type of effect desired, and range from 0.02 to 3 kg of active ingredient per hectare.

[00081] When the active ingredients are used for treating seed, rates of 0.001 to 50 g a.i. per kg, and generally from 0.01 to 10 g per kg of seed are generally sufficient.

[00082] The composition of the invention can be employed in any conventional form, for example in the form of a twin pack, an instant granulate, a flowable formulation, an emulsion concentrate or a wettable powder or surfactant (such as sodium lauryl sulfate and sodium lauryl sulfate salts), in combination with agriculturally acceptable adjuvants. Such compositions may be produced in conventional manner, e.g. by mixing the active ingredients with appropriate adjuvants (diluents or solvents and optionally other formulating ingredients such as surfactants). Also conventional slow release formulations may be employed where long lasting efficacy is intended.

[00083] Particularly formulations to be applied in spraying forms such as water dispersible concentrates or wettable powders may contain surfactants such as wetting and dispersing agents, e.g. the condensation product of formaldehyde with naphthalene sulphonate, an alkylarylsulphonate, a lignin sulphonate, a fatty alkyl sulphate, and ethoxylated alkylphenol and an ethoxylated fatty alcohol.

[00084] A seed dressing formulation is applied in a manner known per se to the seeds employing the combination of the invention and a diluent in suitable seed dressing formulation form, e.g. as an aqueous suspension or in a dry powder form having good

adherence to the seeds. Such seed dressing formulations are known in the art. Seed dressing formulations may contain the single active ingredients or the combination of active ingredients in encapsulated form, e.g. as slow release capsules or microcapsules.

[00085] In general, the formulations include from 0.01 to 90% by weight of active agent, from 0 to 20% agriculturally acceptable surfactant and 10 to 99.99% solid or liquid adjuvant(s), the active agent consisting of at least the compound of formula I, and optionally other active agents, particularly microbides or conservatives or the like. Concentrated forms of compositions generally contain in between about 2 and 80%, generally from between about 5 and 70% by weight of active agent. Application forms of formulation may for example contain from 0.01 to 20% by weight, generally from 0.01 to 5% by weight of active agent. Whereas commercial products will generally be formulated as concentrates, the end user will normally employ dilute formulations.

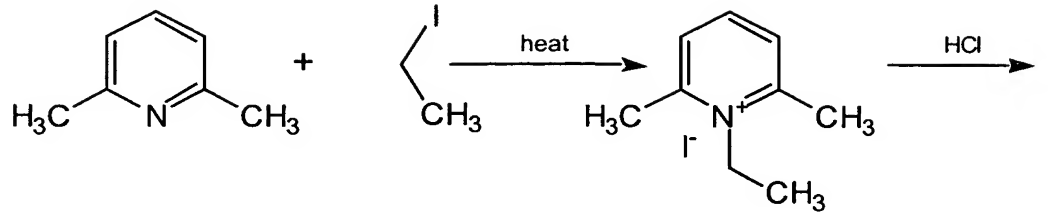
[00086] Additionally, the color of the present compounds may be removed by a type of "bleaching". It is well recognized in the art (cf. for instance B. C. Saunders et al., Peroxidase, London, 1964, p. 10 ff.) that peroxidases act on various amino and phenolic compounds resulting in the production of a color. In view of this, it must be considered surprising that peroxidases (and certain oxidases) may also exert an effect on colored substances in solution such that dye transfer is inhibited. While the mechanism governing the ability of these enzymes to effect dye transfer inhibition has not yet been elucidated, it is currently believed that the enzymes act by reducing hydrogen peroxide or molecular oxygen and oxidizing the colored substance (donor substrate) dissolved or dispersed in the wash liquor, thereby either generating a colorless substance or providing a substance which is not adsorbed to the fabric or building material.

[00087] Additionally, a liquid composition of matter according to the present invention may be formed and may be mixed with and/or diluted by an excipient. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the composition of matter. Various suitable excipients will be understood by those skilled in the art and may be found in the *National Formulary*, 19: 2404-2406 (2000), the disclosure of pages 2404 to 2406 being incorporated by reference herein in their entirety. Preferable excipients include butanedioal and EDTA. Examples of suitable excipients include, but are not limited to, starches, gum arabic, calcium silicate, microcrystalline cellulose, methacrylates, shellac, polyvinylpyrrolidone, cellulose, water, syrup, and methylcellulose. An aqueous medium may include an active ingredient or ingredients, a quantity of one or more surfactants sufficient to dissolve or suspend said active ingredients uniformly throughout the medium and other manufacturing additives as known to

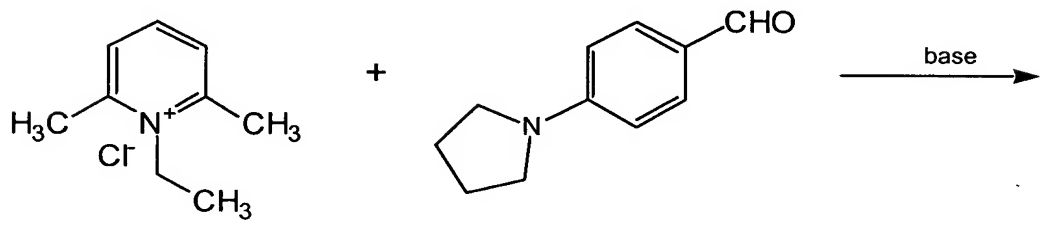
the art. The latter include granulating-binding agents such as gelatin; natural gums, such as acacia, tragacanth; starches, sodium alginate, sugars, polyvinylpyrrolidone; cellulose derivatives such as hydroxypropylmethylcellulose, polyvinyloxoazolidones; pharmaceutical fillers such as lactose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, calcium sulfate, dextrose, mannitol, sucrose; tabletting lubricants if needed such as calcium and magnesium stearate, stearic acid, talc, sterotex (alkaline stearate). The term "aqueous medium" for one ingredient of one of the embodiments of the invention is used within the custom of the art. Primarily, it connotes a water medium, with added water-miscible solvents such as isopropanol or ethanol when needed, to support the active ingredient.

[00088] The present invention is explained in greater detail in the Examples that follow. These examples are intended as illustrative of the invention and are not to be taken are limiting thereof.

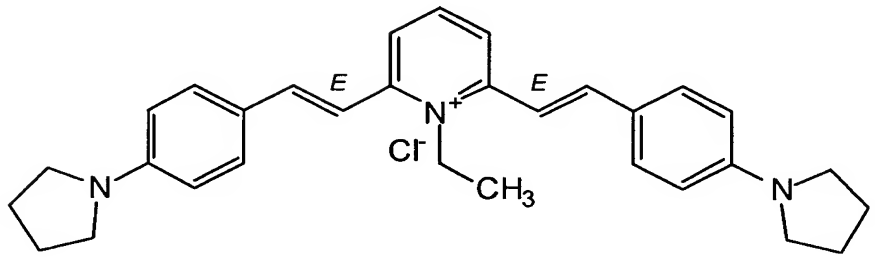
[00089] Example 1: Synthesis of 1-Ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium Chloride (6)



1 (2,6-lutidine) 2 (iodoethane) 3 (2,6-lutidine ethiodide)



4 (2,6-lutidine ethochloride) 5 (aromatic aldehyde)



6

[00090] *Step a: Reaction of 2,6-Lutidine (1) and Iodoethane (2) to Form 2,6-Lutidine Ethiodide (3).* A total of 69.7 grams (0.65 mole) of 2,6-lutidine (1) was combined with 202.8 grams of ethyl iodide (2) and the mixture was heated at 100°C overnight. The reaction mixture was then cooled and the precipitated 2,6-lutidine ethiodide (3) was collected by filtration. The filtrate was reheated to 100°C overnight, then cooled and filtered to recover a second crop of solid 2,6-lutidine ethiodide (3). These two crops were combined, dissolved in hot absolute ethanol and recrystallized. This resultant solid was dissolved in hot ethanol and recrystallized a second time. The purified 2,6-lutidine ethiodide (3) was air dried to constant weight to yield 107.5 grams of desired product. The ^{1}H-NMR was consistent with the desired material and the uncorrected melting point was determined to be 205-206°C.

[00091] *Step b: Conversion of 2,6-Lutidine Ethiodide (3) to 2,6-Lutidine Ethochloride (4).* The 107.5 grams of 2,6-lutidine ethiodide was dissolved in 2.0 liters of methanol and the solution was chilled in an ice-water bath. A total of 220 grams of anhydrous hydrogen

chloride gas was slowly added to the solution via a gas bubbler. An ice-water bath was used to keep the reaction temperature below 30°C during the hydrogen chloride addition. After all the hydrogen chloride had been added, the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated to near dryness and then re-dissolved in 1.0 liter of methanol. A total of 103 grams of anhydrous hydrogen chloride gas was then bubbled into the mixture. After stirring for 10 minutes, the reaction mixture was concentrated to dryness under vacuum to yield 94.3 grams of the desired 2,6-lutidine ethochloride (4).

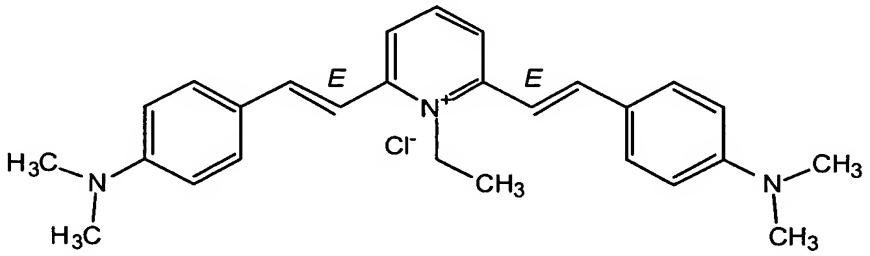
[00092] *Step c: Reaction of 2,6-Lutidine Ethochloride (4) and 4-Pyrrolidinobenzaldehyde (5) to Produce 1-Ethyl-(E,E)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium Chloride (6).*

[00093] A mixture of 30.6 grams (0.22 mole) of 2,6-lutidine ethochloride (4), 75 grams (0.54 mole) of 4-pyrrolidinobenzaldehyde (5), 12 mL piperidine and ca. 2 liters of methanol was heated at reflux overnight. The ^{1}H NMR indicated that no reaction had occurred. No reaction occurred after heating the reaction mixture for an additional 96 hours at reflux. An additional 12mL of piperidine was added and heating at reflux continued. After a total of 120 hours of heating at reflux, some solids began precipitating but ^{1}H NMR indicated that the desired reaction was still incomplete. Another 12 mL of piperidine catalyst was added and the reaction mixture was heated at reflux for an additional 24 hours. The ^{1}H NMR spectrum now indicated the desired reaction was carried to completion. The reaction mixture was slowly cooled to room temperature and the precipitated solid containing 1-ethyl-(E,E)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride (6) was collected by filtration. The solid was triturated and washed with three 100 ml portions of ethyl ether to remove impurities and residual methanol solvent. The solid was air dried and dried under vacuum to constant weight to yield 32.6 grams of red crystalline 1-ethyl-(E,E)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride (6) - high performance liquid chromatography area per cent (HPLC Area%) = 98.1%, ^{1}H NMR (DMSO, d_6); ppm 8.16-8.14 (t,1H); 8.08-8.07 (d,2H); 7.71-7.68 (d,1H); 7.69-7.67 (d,2H,J=8.8Hz); 7.23-7.20 (d,1H); 6.61-6.59 (d,2H,J=8.8Hz); 4.75-4.74 (m,2H); 3.31 (m,2H); 1.98-1.96 (m,2H); 1.48-1.45 (t,3H).

[00094] The reaction filtrate was concentrated to approximately one-half the original volume, 10mL of piperidine was added and the dark reaction filtrate was heated at reflux for 24 hours. ^{1}H NMR spectral analysis indicated that more 1-ethyl-(E,E)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride (6) had formed, possibly by olefinic isomer equilibration. The heat was removed and the reaction mixture was allowed to stir at room temperature for 48 hours, during which time a precipitate formed. The solid was collected by

filtration and was triturated and washed with three 100 ml portions of ethyl ether to remove impurities and residual methanol solvent. The red crystalline solid was air dried and dried under vacuum to constant weight to yield 19.2 grams of additional 1-ethyl-(E,E)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride (6) - HPLC Area% = 97.4%, ^{1}H NMR was consistent with the first crop of product (6).

[00095] Example 2: Synthesis of 1-Ethyl-(*E,E*)-2,6-bis[2-[4-(dimethylamino)phenyl]ethenyl]pyridinium Chloride

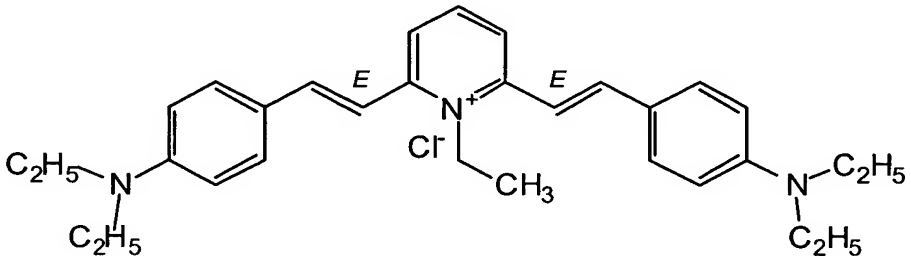


[00096] A mixture of 9.0 grams (0.07 mole) of 2,6-lutidine ethochloride, 23.6 grams (0.16 mole) of 4-dimethylaminobenzaldehyde, 14 mL piperidine and 350 mL methanol was heated at reflux for 77 hours. After 77 hr at reflux, high performance liquid chromatography – mass spectral analysis (LC/MS analysis) indicated that the desired product was present in the reaction mixture. The reaction mixture was slowly cooled to effect precipitation and the precipitated solids were collected by filtration. The solids were triturated and washed with three 100 ml portions of ethyl ether to remove impurities and residual methanol solvent. The solid was air dried and dried under vacuum to constant weight to yield 2.8 grams of red crystalline 1-ethyl-(*E,E*)-2,6-bis[2-[4-(dimethylamino)phenyl]ethenyl]pyridinium chloride - high performance liquid chromatography area per cent (HPLC Area%) = 99.5%, ^{1}H NMR (DMSO, d_6) consistent with the desired product.

[00097] The reaction filtrate was concentrated to approximately one-half the original volume. A total of 10mL of piperidine catalyst was added and the dark solution was heated at reflux for an additional 24 hours. At this point high performance liquid chromatography area per cent analysis (HPLC A% analysis) indicated that more product had formed and the 2,6-lutidine ethochloride starting material was almost gone. The heat was removed and the reaction was concentrated under vacuum to yield a heavy slurry. The precipitated solid was collected by filtration, washed with three 100 ml portions of ethyl ether and the resulting solid was air dried and vacuum dried overnight to yield 13.6 grams of red crystalline 1-ethyl-

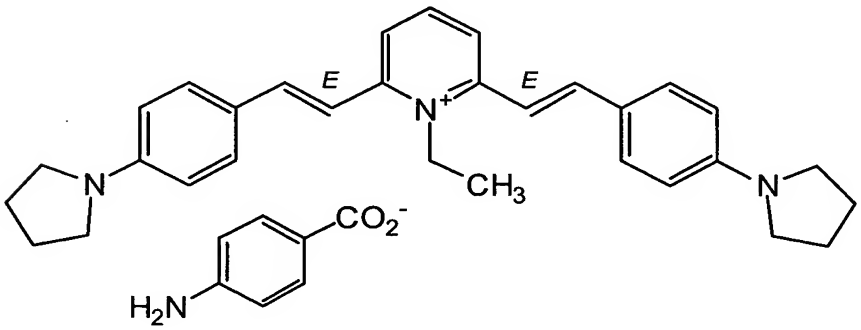
(*E,E*)-2,6-bis[2-[4-(dimethylamino)phenyl]ethenyl]pyridinium chloride - HPLC Area% = 99%, ^{1}H NMR was consistent with the desired product.

[00098] Example 3: Synthesis of 1-Ethyl-(*E,E*)-2,6-bis[2-[4-(diethylamino)phenyl]ethenyl]pyridinium Chloride



[00099] A mixture of 9.0 grams (0.07 mole) of 2,6-lutidine ethochloride, 28.1 grams (0.16 mole) of 4-diethylaminobenzaldehyde, 14 mL piperidine and 350 mL methanol was heated to reflux for 96 hours at which time LC/MS analysis indicated that the desired product was present. The reaction mixture was cooled and concentrated under vacuum to produce a slurry. The solid was collected by filtration and was triturated and washed with three 50 ml portions of ethyl ether. The resulting purified solid was air dried and vacuum dried to yield 17.3 grams of red crystalline 1-ethyl-(*E,E*)-2,6-bis[2-[4-(diethylamino)phenyl]ethenyl]pyridinium chloride - high performance liquid chromatography area per cent (HPLC Area%) = 95%, ^{1}H NMR (DMSO, d_6) was consistent with the desired material and a trace of the starting 4-diethylaminobenzaldehyde present.

[000100] Example 4: Synthesis of 1-Ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium 4-Aminobenzoate Salt



[000101] A total of 52.8g (0.12 mole) of 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium chloride and 18.6 grams (0.12 mole) of the sodium

salt of 4-aminobenzoic acid (sodium salt of p-aminobenzoic acid, Na^+ $PABA^-$) were dissolved in 1.3 liters of methanol and this mixture was allowed to stir at room temperature for 4 days during which time a precipitate formed. The reaction mixture was then filtered and the solid salt was air dried and vacuum dried to yield a first crop of 28.0 grams of 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium 4-aminobenzoate salt (also termed the PABA salt). The filtrate was concentrated under vacuum to produce more precipitate. Isolation of the second crop was effected by filtration followed by air drying and vacuum drying of the solid to afford a second crop of 42.6 grams of 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium 4-aminobenzoate salt (also termed the PABA salt) - high performance liquid chromatography area per cent (HPLC A%) first crop = 99.6% excluding PABA; HPLC A% second crop = 99.9% excluding PABA; ^1H NMR and Mass Spectral analyses for both crops were consistent with structure of the desired material 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium 4-aminobenzoate salt. This product is also named 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium p-aminobenzoate salt or 1-ethyl-(*E,E*)-2,6-bis[2-[4-(pyrrolidinyl)phenyl]ethenyl]pyridinium PABA salt.

[000102] By the methods demonstrated in Examples 1-3, substituted and unsubstituted aromatic aldehydes or substituted and unsubstituted heteroaromatic aldehydes are reacted with substituted and unsubstituted lutidine ethochloride salts, lutidine isobutochloride salts, lutidine methochloride salts, lutidine 1,1,1-trifluoroethochloride salts and the like and with secondary amine catalysts such as piperidine and pyrrolidine in polar protic solvents such as methanol, ethanol, 2-propanol and the like or polar aprotic solvents such as acetonitrile (ACN), dimethyl acetamide (DMA), dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and the like to yield any possible combination of compounds as noted throughout the application and the claims. Applicants have additionally provided numerous compounds shown in FIGs. 1-4 to illustrate some of the possible combinations of the present invention.

[000103] In the following Examples, the "active ingredient" may be any compound of formula (I) as recited above or a pharmaceutically acceptable salt or solvate thereof.

[000104] EXAMPLE 5: Antibacterial Activity

[000105] Solutions of formula I, Stilbazium Chloride, (1% dimethylsulfoxide) were diluted with sterile water, using serial half-step dilutions. Forty microliters of each dilution were then pipetted onto seeded Mueller-Hinton agar plates. The agar plates were then incubated for 24 hours at 35°C and zones of inhibition were then recorded. The Minimum Inhibitory Concentration (MIC) was the lowest concentration of the test material which

produced a zone of inhibition against the organism. The MIC for formula I against a series of organisms is listed in the table below.

Table 1: Anti-bacterial activity of formula I

Strain	MIC
Streptococcus pyogenes	1.0
Streptococcus faecalis	1.0
Streptococcus algalactia	1.0
Staphylococcus aureus	0.3
Bordella bronchiseptica	1.0
Vibrio cholerae	10.0
Pasturella multocida	3.0
E. coli	>100
Pseudomonas aerugenosa	>100

* The data represent the minimal inhibitory concentrations of formula I, in μg/mL, for inhibition of bacterial growth, cultured in vitro.

[000106] EXAMPLE 6: Antifungal activity

[000107] Fungal strains (obtained from ATCC) were grown in Mueller-Hinton broth for 18 hours at 35°C. Plates were then seeded with the broth culture and allowed to air-dry at room temperature (22°.) for about 10-15 minutes. Forty microliters of formula I (in 1% dimethylsulfoxide) and serial half-step dilutions in water were then pipetted onto the seeded Mueller-Hinton agar plates. The plates were then incubated for 24 hours at 35.degrees C. and zones of inhibition were then recorded. The Minimum Inhibitory Concentration (MIC) was the lowest concentration of formula I which produced a zone of inhibition against the organism. The following table lists the antifungal activity of formula I against various fungal strains.

[000108] Table 2: Inhibition of yeast and fungal growth by Formula I *in vitro*

Organism	MIC
Candida albicans	<0.006
Candida tropicalis	<0.4
Cryptococcus neoformans	<0.4
Saccharomyces cervisciae	<0.4
Aspergillus fumigatus	<0.006
Aspergillus flavus	6.25
Fusarium solani	<0.4
Rhizopus arrihizus	6.25
Microsporidium canis	1.6
Microsporidium gypseum	1.6
Trichophyton equinium	1.6
Trichophyton mentagrophyt	1.6
Trichophyton rubrum	1.6
Epidermophyton floccsum	1.6

* The data represent the minimal inhibitory concentrations of formula I, in μg/mL, for inhibition of bacterial growth, cultured in vitro.

[000109] EXAMPLE 7

[000110] ***In vitro*** **screening**

[000111] A stock solution of each compound was prepared in DMSO at a concentration of 10,000 ppm a.i.. Further dilutions were prepared with water. The test was conducted at the following concentrations: 125, 31, 8, 21, 0.5 and 0.125 ppm a.i.. Spore suspensions of the following fungi were prepared: *Alternaria solani, Botrytis cinerea, Cochiobolus mijabeanus, Colletotrichum lagenarium, Fusarium culmorum, Phytophthora infestans, Pyrenophora teres, Pyricularia oryzae, Rhizoctonia solani* and *Septoria tritici.*

[000112] The test was conducted in microtiter plates and for each fungus and each concentration, 3 wells were prepared. Incubation of the inoculated plates was carried out at 18°C for 7 days. After this time, the optical density of the mycelium developed in each well was measured at 405 nm. The data produced allowed an assessment of the IC 90 value (the concentration at which the fungal growth was reduced by at least 90% compared to the control).

[000113] ***In vivo*** **– detached leaf assay**

[000114] In this model, detached leaves of appropriate host plants were placed on water agar. The leaves were treated with 20 μl cm^2 of a 15 ppm a.i. solution of each compound, which had been prepared from the 10,000 ppm a.i. stock solution in DMSO. The treated leaves were allowed to dry for 24 h, after which they were inoculated with the following fungal species (host plant in brackets); an exception was wheat brown rust (Puccinia triticina) where the inoculation of the leaves had been made 24 h before application of the test compounds: *Blumeria graminis f.sp. tritici* (wheat), *Fusarium culmorum* (barley), *Phaeosphaeria nodorum* (wheat), *Phytophthora infestans* (tomato), *Puccinia triticina* (wheat) *and Pyricularia oyrzae* (rice).

[000115] The leaves were subsequently incubated at 18°C with a 12 h photo period. The incubation period was up to 7 days. There were 3 replicates.

[000116] *In vivo* - glasshouse screening

[000117] The compounds were sprayed to run-off onto the test plants at 250, 63 and 16 ppm a.i., inoculation of the treated plants took place 24 h after treatment, as before the exception being wheat brown rust, where inoculation took place 24 h before treatment. The following pathogen/host plant combinations were included in the trial: *Alternaria solani /*

tomato, *Botrytis cinerea* / bell pepper, *Phytophthora infestans* / tomato and *Puccinia triticina* / wheat.

[000118] Incubation followed under climatic conditions favourable for the development of the fungal pathogen. Disease development was assessed 7 days after inoculation.

[000119] Overall Results

[000120] The majority of the tested compounds showed a broad in vitro activity, which was, in some cases, also seen at very low concentrations.

[000121] Under glasshouse conditions and using intact plants, a limited degree of activity could be seen, at a high concentration (250 ppm a.i.) tested. Activity was shown in *Alternaria solani* and *Phytophthora infestans*.

[000122] EXAMPLE 8

[000123] Stilbazium iodide was tested against a panel of plant relevant mold stains. A stock solution of the compound was prepared in DMSO at a concentration of 10,000 ppm a.i. Further dilutions were prepared with water. The test was conducted at the following concentrations: 125, 31, 8, 21, 0.5 and 0.125 ppm a.i. Spore suspensions of the fungi were prepared. The test was conducted in microtiter plates and for each fungus and each concentration, 3 wells were prepared. Incubation of the inoculated plates was carried out at 18°C for 7 days. After this time, the optical density of the mycelium developed in each well was measured at 405 nm.

[000124] The data produced, shown in Table 3, allowed an assessment of the IC 90 value (the concentration at which the fungal growth was reduced by at least 90% compared to the control).

[000125] Table 3

Organism	Plant Relevance	IC90
Alternaria solani	Potato	>125
Botrytis cinerea	Vegetable	0.5
Cochliobolus mijabeanus	Corn	>125
Colletotrichum lagenarium	Mellons	31
Fusarium culmorum	Wheat Head	>125
Phytophthora infestans	Tomato	2
Pyrenophora teres	Barley	31
Pyricularia oryzae	Rice	8
Rhizoctonia solani	Rice Sheath	2
Septonia tritici	Wheat Leaf	2

[000126] EXAMPLE 9

[000127] The data shown below in Table 4 illustrates various bacteria and fungi that can be treated by stilbazium compounds. The data illustrates the overall effectiveness of various stilbazium compounds.

[000128] Table 4

Species	Isolate #	MIC 80%	MIC 100%	MFC
Alternaria species	128.89	6.25	12.5	>100
Aspergillus flavus	112.96	3.12	6.25	6.25
Aspergillus flavus	194.99	3.12	3.12	12.5
Aspergillus flavus	107.96	6.25	12.5	25
Aspergillus flavus	141.88	12.5	25	25
Aspergillus flavus	178.03	12.5	25	>25
Aspergillus flavus	173.03	25	25	>25
Aspergillus fumigatus	168.95	3.12	6.25	>25
QC A. fumigatus	168.95	3.12	6.25	>100
QC A. fumigatus	168.95	3.12	6.25	>100
Aspergillus fumigatus	111.02	3.12	6.25	12.5
Aspergillus fumigatus	153.90	12.5	25	25
Aspergillus fumigatus	182.99	12.5	25	>25
Aspergillus sydowii	165.02	0.78	1.56	3.12
Aspergillus versicolor	120.02	1.56	3.12	6.25
Bipolaris spicifera	155.89	3.12	3.12	>100
Candida albicans	A39	0.39	0.39	0.39
Candida albicans	117.00	0.39	0.39	0.39
QC C. albicans	117.00	1.56	1.56	3.12
QC C. albicans	117.00	3.12	3.12	6.25
Candida albicans	117.00	0.78	1.56	3.12
Candida albicans	116.98	0.39	0.39	1.56
Candida albicans	126.97	0.39	0.78	0.78
Candida albicans	149.97	0.39	0.39	0.78
Candida albicans	159.95	0.39	0.39	1.56
Candida albicans	156.97	1.56	1.56	1.56
Candida albicans	203.03	1.56	1.56	3.12
Candida albicans	204.03	1.56	1.56	1.56
Candida albicans	205.03	1.56	1.56	6.25
Candida albicans	206.03	3.12	3.12	12.5
Candida albicans	202.03	3.12	3.12	3.12

Candida parapsilosis	110.01	0.78	0.78	3.12
Candida parapsilosis	ATCC 22019	0.78	0.78	3.12
Candida parapsilosis	109.96	1.56	1.56	3.12
Candida parapsilosis	118.02	1.56	1.56	6.25
Candida parapsilosis	123.00	1.56	1.56	6.25
Chaetomium species	T 217	1.56	3.12	>100
Cryptococcus neoformans	H99	0.012	0.024	1.56
Curvularia lunata	141.90	1.56	3.12	>100
Curvularia lunata	110.90	3.12	3.12	>100
Curvularia lunata v. aeria	104.89	3.12	6.25	>100
Curvularia lunata	146.90	6.25	6.25	>100
Penicillium aurantiogriseum	135.02	6.25	12.5	>100
Penicillium chrysogenum	119.02	0.78	0.78	12.5
Rhizopus oryzae	172.86	1.56	6.25	>100
Rhizopus oryzae	182.88	3.12	6.25	>100
Rhizopus oryzae	318.86	3.12	6.25	>100
Rhizopus oryzae	117.89	6.25	6.25	12.5
Rhizopus oryzae	127.88	12.5	12.5	>25
Rhizopus oryzae	181.88	12.5	12.5	>25
Rhodotorula mucilaginosa	213.03	1.56	3.12	6.25
Rhodotorula mucilaginosa	207.03	3.12	3.12	3.12
Rhodotorula mucilaginosa	209.03	3.12	6.25	6.25
Rhodotorula mucilaginosa	210.03	3.12	3.12	3.12
Rhodotorula mucilaginosa	211.03	6.25	6.25	6.25

[000129] In the specification, there has been disclosed typical preferred embodiments of the invention and, although specific terms are employed, they are used in a generic and descriptive sense only and not for purposes of limitation of the scope of the invention being set forth in the following claims.